

Sleep and Sleep Electroencephalogram in Depressed Patients Treated With Phenzelzine

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Background: The beneficial effect of antidepressant interventions has been proposed to depend on suppression of rapid eye movement (REM) sleep or inhibition of electroencephalographic (EEG) slow-wave activity (SWA) in non-REM sleep. Use of the monoamine oxidase inhibitor phenzelzine sulfate can eliminate REM sleep. We studied the relation between REM sleep suppression and antidepressant response and the effect of phenzelzine therapy on sleep EEG power spectra.

Methods: Open-labeled prescriptions of 30 to 90 mg of phenzelzine were given to 11 patients with major depressive disorder (6 men and 5 women; mean age, 41.4 years); all were physically healthy. Mood, dream recall, sleep, sleep EEG, and ocular and muscular activity during sleep were studied before treatment and during the third and fifth weeks of pharmacotherapy.

Results: Six patients remitted from depression, 2 responded partially, and 3 showed no antidepressant response. Independent from clinical response, REM sleep was dramatically suppressed. On average, only 4.9 minutes of REM sleep was observed in treatment week 5, and it was completely absent in 6 patients. This effect was compensated for by increased stage 2 sleep. In non-REM sleep, EEG power was higher than at baseline between 16.25 and 25 Hz. Slow-wave activity (power within 0.75-4.5 Hz) and the exponential decline of SWA during sleep were not affected.

Conclusions: Antidepressant response to phenzelzine treatment does not depend on elimination of REM sleep or inhibition of SWA in non-REM sleep. In depressed patients, REM sleep is regulated independently from non-REM sleep and can be manipulated without altering the dynamics of SWA.

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NORMAL SLEEP of healthy individuals consists of distinct non-rapid eye movement (REM) and REM sleep episodes alternating with ultradian periodicity of 80 to 120 minutes.¹⁻³ REM sleep is identified by electroencephalographic (EEG) desynchronization, complete atonia in antigravity muscles (electromyogram [EMG]), and regularly occurring rapid eye movements (electro-oculogram [EOG]).⁴⁻⁷ Non-REM sleep is characterized by synchronized EEG activity and absence of rapid eye movements. Thus, EEG frequencies less than approximately 15 Hz and tonic EMG activity exhibit higher values in non-REM sleep and lower values in REM sleep.^{8,9} An opposite modulation by the non-REM/REM sleep cycles is observed for higher EEG frequencies and rapid eye movements.^{1,8}

According to the 2-process model, the timing of sleep and wakefulness is regulated by the interaction of a homeostatic, sleep-wake-dependent process S and a cir-

cadian, sleep-wake-independent process C.¹⁰ The homeostatic facet of sleep regulation has been investigated extensively by the spectral analysis of the sleep EEG. Compelling evidence^{11,12} suggests that slow-wave activity (SWA) (power within 0.75-4.5 Hz) depends on the duration of previous sleep and wakefulness and may represent a correlate of non-REM sleep intensity. Largely independent from endogenous circadian phase, maximum SWA is present in the first hours of sleep and declines across consecutive non-REM sleep episodes.¹³ In contrast, REM sleep depends on homeostatic and circadian factors.^{13,14} Under normal entrained conditions, the percentage of REM sleep within non-REM/REM sleep cycles tends to increase toward the end of the night. Approximately 18% to 25% of total sleep time is usually spent in REM sleep.

Alterations of sleep architecture are common in patients with depression.¹⁵ Specifically, many depressed patients experience a short latency to REM sleep and a high density of rapid eye movements dur-

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PATIENTS AND METHODS

PATIENTS

Patients with major depressive disorder were recruited by the University of California at San Diego Mental Health Clinical Research Center, San Diego, via advertisements for individuals with depression. After telephone screening, respondents were administered the Structured Clinical Interview for DSM-IV by a trained staff member of the Mental Health Clinical Research Center and were evaluated by medical and psychiatric history, physical examination, standard laboratory tests (chemistry panel, complete blood cell count, human immunodeficiency virus screen, urinalysis, and drug screen), and electrocardiography. Severity of depression was assessed with the Hamilton Rating Scale of Depression (HRSD), the Beck Depression Inventory, and the Profile of Mood States. All diagnoses were presented to and arrived at by consensus conferences of the Mental Health Clinical Research Center. Patients with current alcohol or substance abuse, bipolar disorder, recent or current major medical comorbid disorder, or the inability to comply with the MAO inhibitor diet³⁹ were excluded. Subsequently, patients were screened by polysomnography in the sleep laboratory to exclude sleep apnea and nocturnal myoclonus. Written informed consent was obtained before screening.

Twelve patients were enrolled in this depression treatment study. They were paid for the sleep studies in the laboratory. One patient did not meet all inclusion criteria the morning after the baseline night (BL), and his data were excluded from all analyses. All remaining patients (5 women and 6 men; mean \pm SD age, 41.4 \pm 7.3 years) had a minimum score of 14 on the 17-item HRSD for at least 1 week before BL (**Table 1**). The mean \pm SD number of depressive episodes was 3.0 \pm 1.6. The current episode was the first for 2 patients (patients 01

and 14). The mean \pm SD duration of the current episode was 203.8 \pm 350.6 weeks. It lasted 6 to 150 weeks in 9 patients and 1144 weeks in patient 14 and 572 weeks in patient 18. The mean \pm SD age at first onset of depression was 20.0 \pm 9.1 years. Except for patients 13 and 15 being treated for hypertension, no patient had a physical condition. Patient 12 did not disclose the use of a centrally acting agent, ie, St John's wort, until completion of the study. None of the patients had been treated with any psychoactive or sleep medication within at least 2 weeks before initiation of phenelzine treatment or received additional psychotherapy during the study. Four patients were taking minor analgesics occasionally (Table 1). On recording days, moderate caffeine consumption was limited to the morning hours. No alcohol was permitted for the duration of the study, and patients were instructed to keep a regular sleep-wake cycle, with sleep scheduled at their habitual bedtime.

PROCEDURE

The study protocol was approved by the local institutional review boards of the University of California at San Diego and the Veterans Administration Medical Research Foundation, San Diego. In each patient, 3 experimental nights preceded by at least 1 adaptation night were recorded in the completely darkened bedrooms of the sleep laboratory. Adaptation nights were excluded from analyses. The first experimental night served as a drug-free BL. Open-labeled treatment with phenelzine was initiated within 3 days after the BL. An initial dose of 15 mg of phenelzine was increased as tolerated and needed individually to 30 to 90 mg/d by a psychiatrist (E.B.R., B.J.S., J.R.K., or M.H.R.) blind to the sleep EEG findings (Table 1). Follow-up polysomnography was scheduled during weeks 3 and 4 (P3) and 5 and 6 (P5) of phenelzine treatment. Because of a back injury experienced in treatment week 5, night P5 of patient 16 was recorded in week 9 after initiation of treatment.

Continued on next page

ing REM sleep.¹⁶⁻¹⁸ Disinhibition of REM sleep may, therefore, be associated with the illness. Because many antidepressant drugs reduce REM sleep, suppression of REM sleep has been proposed to underlie antidepressant efficacy.^{19,20} Selective REM sleep deprivation in healthy individuals, however, inhibits SWA in non-REM sleep.²¹⁻²³ Accordingly, reduced non-REM sleep intensity may represent the final common pathway of antidepressant therapies, which increase the pressure for REM sleep.²⁴ Only a few studies have investigated the effects of antidepressant therapy on the sleep EEG, and inconsistent findings were reported.²⁵ One study²⁶ suggested that use of the tricyclic antidepressant clomipramine hydrochloride induced the redistribution of delta power during the initial part of the night. The authors implied that improvement of depression might be related to the normalization of process S during sleep.

Monoamine oxidase (MAO) inhibitors are capable of virtually abolishing REM sleep in animals and humans.²⁷⁻²⁹ Phenelzine sulfate, a classical MAO inhibitor, has proven antidepressant efficacy and eliminates REM sleep in a dose-dependent manner.³⁰⁻³⁵ Its effects on sleep intensity and the ultradian variation of EEG frequencies are unknown. The main goals of the present study were as follows: (1) To investigate the time course of SWA in

the absence of REM sleep. Based on the 2-process model, we hypothesized that the dynamics of SWA would not be altered by the elimination of REM sleep.³⁶ (2) To test whether suppression of REM sleep and reduction of non-REM sleep intensity are associated with antidepressant mechanisms. Because antidepressant agents have inconsistent effects on REM sleep and SWA,^{25,37} we predicted that the antidepressant response to phenelzine treatment would be independent from its effects on REM sleep or SWA. (3) Given that dreaming may be preferentially associated with REM sleep,³⁸ we collected daily dream reports and predicted that dream recall would decrease when REM sleep was eliminated.

RESULTS

TREATMENT RESPONSE AND DOSE OF PHENELZINE

The total score of the HRSD (24 items) decreased significantly with treatment ($F_{2,20} = 12.0$; $P < .004$). Mean \pm SEM HRSD values dropped from 23.5 \pm 1.3 at BL to 14.5 \pm 2.7 ($P < .004$, 2-tailed paired t test) at P3 and 12.5 \pm 2.7 ($P < .001$) at P5. At P5, 6 of the 11 patients were treatment responders, with an HRSD score of 9 or lower

Symptoms of depression were rated within 3 days of each experimental night. In addition, patients were seen at 1-week intervals for assessment of vital signs, mood ratings, subjective sleep quality, dream recall, and medication adverse effects. Patients were asked to keep a sleep and dream log throughout the treatment period.

POLYGRAPHIC RECORDINGS

The EEG (data from the C3A2 derivation are reported here), EOG, submental EMG, and electrocardiographic data were recorded by a portable polygraphic amplifier (PS1; Institute of Pharmacology and Toxicology, University of Zürich, Zürich, Switzerland). The signals were digitized and transmitted via fiber optic cables to a notebook computer with a digital signal processor board. The analogue signal was conditioned by a high-pass filter (-3 dB at 0.16 Hz) and a low-pass filter (-3 dB at 70 Hz and approximately -28 dB at 256 Hz). Data were sampled with a frequency of 512 Hz, digitally filtered (EEG, EOG, and electrocardiogram: low-pass finite impulse response filter at 30 Hz; EMG: band-pass finite impulse response filter at 20 and 50 Hz), and stored on hard disk with a resolution of 128 Hz. Power spectra for consecutive 4-second epochs, weighted by application of a 10% cosine window, were computed by a Fast-Fourier transform routine, resulting in a frequency resolution of 0.25 Hz. Values of adjacent 0.25-Hz bins were averaged into 0.5-Hz (0.25-5 Hz) and 1-Hz (5.25-25 Hz) bins, and those greater than 25 Hz were omitted. Sleep stages were visually scored for consecutive 20-second epochs according to the criteria of Rechtschaffen and Kales.² Power spectra of 5 consecutive 4-second epochs were averaged and matched with the sleep scores. Four-second epochs with movement- and arousal-related artifacts were visually identified and eliminated.

DATA ANALYSIS AND STATISTICS

Visually scored sleep variables, frequency of dreams, EEG power spectra, and the time course of EEG frequencies and the variance of the EMG, EOG, and EEG signals were analyzed. At BL, non-REM/REM sleep cycles were defined as in previous studies.⁴⁰ For time course analyses, individual non-REM and REM sleep episodes were subdivided into an equal number of time bins of approximately 5-minute duration. Because of different mean episode durations, this procedure yielded 14, 17, and 16 time bins for the first 3 non-REM sleep periods and 3, 4, and 6 time bins for the first 3 REM sleep periods. In P5, the first 5 hours after sleep onset were subdivided into 60 five-minute intervals regardless of the sleep state. As at BL, however, EEG, EMG, and EOG values during movement time and wakefulness were excluded from the analyses. In addition, 20-second epochs of sleep containing short arousals or pulse artifacts in the EMG were excluded from EMG analyses. Because of technical problems, the EMG data of patient 05 were lost in BL, and the EMG analyses were carried out in 10 patients only.

For data analyses, SAS statistical software (SAS Institute Inc, Cary, NC) was used. Effects of phenelzine treatment were assessed using Friedman statistics⁴¹ (visually scored sleep variables) or 1- and 2-way repeated-measures analyses of variance (ANOVAs) with multiple within and between factors, as described in the "Results" section. For within factors, the Greenhouse-Geisser degrees of freedom⁴² were computed for statistical inference, but the original degrees of freedom are reported. Pairwise comparisons between nights were performed with 2-tailed Wilcoxon matched-pairs signed rank tests (visually scored sleep variables) or 2-tailed paired *t* tests. The significance level was set at $\alpha = .05$. To approximate a normal distribution, absolute EEG power values, EMG activity, and EOG/EEG variance were log transformed before statistical tests were performed.

and a reduction of 50% or more from the initial HRSD value (Table 1). Two of the other 5 patients were partial responders (patients 11 and 13); their HRSD scores had decreased 36% and 46%, respectively. The remaining 3 patients did not show improvement in depressive symptoms. The final average daily dose of phenelzine was 65 mg for the 6 responders, 45 mg for the 2 partial responders, and 60 mg for the 3 nonresponders.

VISUALLY SCORED SLEEP VARIABLES AND DREAM RECALL

The major change in sleep induced by phenelzine consisted of a gradual and pronounced suppression of REM sleep (Table 2). In P5, REM sleep was completely eliminated in 6 patients: 2 of 6 responders (patients 12 and 14) and 4 of 5 nonresponders (patients 05, 11, 13, and 18). During the first 5 hours after sleep onset, no REM sleep occurred in 8 patients. In the remaining 3 patients, a short duration of REM sleep was left: 2 responders, patients 01 (16.7 minutes) and 16 (5.3 minutes), and 1 nonresponder, patient 06 (0.7 minutes). Spearman rank correlation analysis revealed no significant correlation between drug-induced reduction of REM sleep and change in the total HRSD score.

Suppression of REM sleep was compensated in part by an increase in stage 2 sleep (duration and percentage) (Table 2). No significant differences between BL and the treatment nights were observed for total sleep time, sleep efficiency, sleep latency, slow-wave sleep, and wakefulness after sleep onset.

Patients reported remembering at least 1 dream in a mean \pm SEM 23.2% \pm 9.3% of nights in treatment week 1 ($n = 11$), in 14.5% \pm 7.6% of nights in week 2 ($n = 10$), in 14.8% \pm 7.6% of nights in week 3 ($n = 10$), in 10.5% \pm 4.5% of nights in week 4 ($n = 10$), and in 11.7% \pm 5.3% of nights in week 5 ($n = 9$). Treatment had a different effect on dream recall in antidepressant responders and nonresponders (including partial responders). A 2-way ANOVA with the between factors "group" (responders and nonresponders) and "week" (1-5) disclosed a significant group \times week interaction ($F_{4,49} = 2.6$; $P = .05$; group: $F_{1,49} = 6.2$; $P < .02$; week: $F_{4,49} = 0.4$; $P > .7$). Responders recalled significantly fewer dreams after morning awakening in weeks 4 and 5 than in week 1, whereas nonresponders showed no significant change (Table 3).

EEG POWER SPECTRA

Mean all-night EEG power spectra in BL, P3, and P5 were calculated in non-REM sleep (stages 2, 3, and 4)

Table 1. Patient Characteristics*

Patient No./ Sex/Age, y	MDD	Secondary SCID Diagnoses	Condition	HRSD Score	Phenelzine, mg/d	Concomitant Medication
01/M/43.9	Single episode, severe	None	BL	14/21	0	None
			P3	8/10	60	Multivitamins
			P5	6/8	75	None
02/F/35.8	Recurrent, moderate	GAD	BL	16/22	0	Ferrous sulfate
			P3	8/8	30	Aspirin
			P5	7/7	45	None
05/M/39.2	Recurrent, moderate	ADSFR and CoDSFR	BL	15/15	0	None
			P3	16/17	75	None
			P5	13/15	90	None
06/M/29.4	Recurrent, severe	SpecPH	BL	19/25	0	Minoxidil, finasteride, and loperamide hydrochloride
			P3	22/30	45	Minoxidil, finasteride, and loperamide hydrochloride
			P5	21/25	60	Minoxidil, finasteride, and loperamide hydrochloride
11/M/42.2	Recurrent, moderate	Dysthymia	BL	15/25	0	None
			P3	10/15	45	None
			P5	11/16	45	None
12/M/53.5	Recurrent, moderate	ADSFR and CaDSFR	BL	14/21	0	St John's wort and aspirin
			P3	4/6	60	St John's wort
			P5	6/6	90	St John's wort
13/F/48.8	Recurrent, moderate	None	BL	19/26	0	Hydrochlorothiazide and captopril
			P3	22/23	75	Hydrochlorothiazide and captopril
			P5	10/14	45	Hydrochlorothiazide and aspirin
14/M/37.5	Single episode, severe	ADSFR, CaDSFR, and CoDSFR	BL	20/27	0	Multivitamins
			P3	15/19	60	Multivitamins
			P5	8/9	75	Multivitamins
15/F/31.7	Recurrent, moderate	GAD	BL	15/19	0	Hydrochlorothiazide
			P3	3/3	60	None
			P5	2/2	60	None
16/F/44.8	Recurrent, moderate	PDWA, ADEPR, and PTSDFR	BL	20/26	0	None
			P3	4/4	45	None
			P5	4/4	45	None
18/F/48.0	Recurrent, severe	GAD, PDWA, SpecPH, and SocPH	BL	23/31	0	Estrogen, multivitamins, and ginkgo biloba
			P3	17/24	30	Estrogen and multivitamins
			P5	23/31	30	Estrogen, multivitamins, and ibuprofen

*MDD indicates major depressive disorder (primary Structured Clinical Interview for DSM-IV [SCID] diagnosis); HRSD, Hamilton Rating Scale of Depression; GAD, generalized anxiety disorder; ADSFR, alcohol dependence in sustained full remission; CoDSFR, cocaine dependence in sustained full remission; SpecPH, specific phobia; CaDSFR, cannabis dependence in sustained full remission; PDWA, panic disorder with agoraphobia; ADEPR, alcohol dependence in early partial remission; PTSDFR, posttraumatic stress disorder in full remission; SocPH, social phobia; BL, drug-free baseline night; P3, weeks 3 and 4; and P5, weeks 5 and 6.

(Figure 1A). Statistical analyses revealed no significant phenelzine-induced changes in frequencies below 15 Hz. In contrast, EEG power was higher in P5 than in BL and P3 in the entire 16.25- to 25-Hz band.

In Figure 1B, EEG power values in each frequency bin in non-REM sleep in the second, third, and fourth 90-minute intervals after sleep onset are expressed relative to the corresponding value in the first 90-minute interval. A 2-way repeated-measures ANOVA on absolute power values with the within factors "treatment" (BL, P3, and P5) and "90-minute interval" (1-4) confirmed the significant effect of phenelzine treatment on all bins in the beta frequency range (16.25-25 Hz; minimum $F_{2,20}=4.56$; $P<.03$). In BL, P3, and P5, power in

the delta and theta bands decreased over consecutive intervals. ANOVA revealed significant effects of the factor "interval" between 0.25 and 7 Hz (minimum $F_{3,30}=12.37$; $P<.001$) and between 9.25 and 17 Hz (minimum $F_{3,30}=4.6$; $P<.04$). No significant treatment \times interval interaction was detected for any frequency bin.

DYNAMICS OF 1-HZ EEG FREQUENCY BANDS DURING SLEEP

To characterize the effect of phenelzine treatment on the ultradian modulation of EEG frequencies during sleep, the time course of 1-Hz frequency bands between 0.25

Table 2. Sleep Variables Derived From Visual Scoring*

Variable	BL	P3	P5	F	P
Lights-out, h.min ± min	22.40 ± 9	22.47 ± 14	22.52 ± 17	0.4	.66
Lights-on, h.min ± min	6.21 ± 4	6.28 ± 8	6.16 ± 11	0.7	.52
Time in bed, min	461.2 ± 8.0	460.1 ± 13.9	450.8 ± 15.6	0.7	.70
Sleep episode, min	433.1 ± 10.1	438.2 ± 14.1	421.4 ± 16.8	0.7	.70
Total sleep time, min	388.0 ± 11.9	382.7 ± 17.1	361.2 ± 20.7	1.6	.44
Sleep efficiency, %†	84.4 ± 2.9	83.7 ± 3.9	79.9 ± 3.1	3.5	.18
Sleep latency, min‡	23.5 ± 6.5	15.5 ± 2.3	18.8 ± 4.1	2.2	.34
REM sleep, min§	70.6 ± 6.6	28.0 ± 8.2¶	4.9 ± 2.7#	18.2	<.001
Stage 2, min	236.9 ± 9.6	269.4 ± 17.3	272.6 ± 15.7¶	8.9	.01
Slow-wave sleep, min	40.8 ± 10.9	55.2 ± 15.2	51.8 ± 15.2	4.4	.11
WASO, min	44.5 ± 13.5	58.6 ± 19.4	66.2 ± 11.2	5.6	.06
REM sleep, %†§	18.1 ± 1.5	6.8 ± 1.8¶	1.3 ± 0.8#**	16.5	<.001
Non-REM sleep stage, %†					
1	10.3 ± 0.8	7.9 ± 1.1	8.7 ± 1.7	5.1	.08
2	61.5 ± 2.7	70.7 ± 4.0¶	76.3 ± 3.5#	10.4	.01
3	5.0 ± 1.2	7.1 ± 2.0	8.2 ± 2.4	2.6	.27
4	5.2 ± 1.9	7.5 ± 2.7	5.4 ± 1.9	1.3	.53
Slow-wave sleep, %†	10.2 ± 2.7	14.6 ± 4.3	13.7 ± 4.1	6.0	.05

*Data are given as mean ± SEM of 11 patients. BL indicates drug-free baseline night; P3, treatment weeks 3 and 4; P5, treatment weeks 5 and 6; REM, rapid eye movement; WASO, wakefulness after sleep onset; and F, Friedman 1-way repeated-measures analysis of variance with factor "treatment" (df = 2).

†Percentages are expressed per total sleep time (TST) except for sleep efficiency, which represents the percentage of TST per time in bed.

‡Time from lights-out to the first occurrence of stage 2.

§The REM sleep was present in 9 patients in P3 and in 6 patients in P5.

¶Stages 3 + 4.

||P < .05 compared with BL (2-tailed Wilcoxon matched-pairs signed rank test).

#P < .001.

**P < .02.

Table 3. Dream Recall in Antidepressant Responders and Nonresponders During Phelzine Treatment*

Week	Responders (n = 6)	Nonresponders (n = 5)
1	40.1 ± 13.7	2.9 ± 2.9
2	26.2 ± 13.8	2.9 ± 2.9
3	26.2 ± 13.6	3.3 ± 3.3
4	14.3 ± 6.4†	6.7 ± 6.7
5	3.3 ± 3.3†	22.1 ± 9.1

*Data are given as mean ± SEM percentage of nights per week in which patients reported to remember at least 1 dream.

†P < .05 compared with week 1 (2-tailed paired t test).

and 25 Hz was analyzed in BL and P5 for consecutive 5-minute intervals during the first 5 hours after sleep onset. **Figure 2** illustrates relative EEG power, expressed as a percentage of the corresponding all-night mean value in non-REM sleep (stages 2, 3, and 4) as a function of time and frequency. Ultradian modulation by the non-REM/REM sleep cycles was present in virtually all 1-Hz frequency bins in BL. Frequencies below 15 Hz were high in non-REM sleep and low in REM sleep. Beta frequencies (>16 Hz) were highest shortly after sleep onset and in the first REM sleep period. No ultradian variation was present in P5. A cluster of high power in delta and theta frequencies (approximately 1-7 Hz), however, existed in the first hour after sleep onset (Figure 2). A 2-way ANOVA with the between factors "treatment" (BL and P5) and "5-minute time bin" (1-60) revealed significant main effects for all 1-Hz frequency bins (treatment: minimum $F_{1,1266} = 5.6$; $P < .02$; time bin: minimum $F_{59,1266} = 1.4$; $P < .03$) except for the 16-Hz bin, which did not show a treat-

ment effect. A significant treatment × time bin interaction was observed for all 1-Hz bins less than 22 Hz (minimum $F_{59,1266} = 1.4$; $P < .02$).

DYNAMICS OF SWA

In BL and P5, relative SWA (power within 0.75-4.5 Hz) exhibited a maximum value within the first hour after sleep onset and declined thereafter (**Figure 3A**). Whereas the typical ultradian modulation was present in BL, SWA decreased continuously in the absence of REM sleep in P5. The different time course was confirmed statistically by a 2-way ANOVA with the between factors "treatment" (BL and P5) and "5-minute time bin" (1-60), which revealed highly significant main effects (treatment: $F_{1,1262} = 223.4$; $P < .001$; time bin: $F_{59,1262} = 31.9$; $P < .001$) and a significant interaction (treatment × time bin: $F_{59,1262} = 11.9$; $P < .001$).

The decline in SWA was further analyzed across the first 3 non-REM sleep episodes in BL and across the first three 90-minute intervals after sleep onset in P5. A 2-way repeated-measures ANOVA with the within factors "treatment" (BL and P5) and "interval" (1-3; non-REM episodes or 90-minute intervals) revealed a significant effect of "interval" ($F_{2,20} = 27.0$; $P < .001$) yet no effect of "treatment" or a significant treatment × interval interaction (**Figure 4**). In both nights, linear regression analysis on logarithmic relative SWA values disclosed significant correlation coefficients, indicating an exponential decline in SWA (BL: $r^2 = 0.997$; P5: $r^2 = 0.997$; $P < .04$). Slopes and intercepts of the 2 regression lines did not differ.

DYNAMICS OF EMG ACTIVITY AND EOG/EEG VARIANCE DURING SLEEP

The median of all 20-second values of the variance of the EMG signal during sleep (stages 1, 2, 3, and 4 and REM sleep) served as a measure of nocturnal tonic EMG activity.⁹ Tonic EMG activity was significantly higher in P5 than in BL (5.9 ± 0.8 vs 1.9 ± 0.2 μV ; $P < .001$, 2-tailed paired t test). The dynamics of relative EMG values during sleep were analyzed in the same way as described for SWA. A 2-way ANOVA with the between factors "treatment" (BL and P5) and "5-minute time bin" (1-60) on relative EMG values revealed a significant effect of "time bin" ($F_{59,1118} = 4.1$; $P < .001$) and a significant treatment \times time bin interaction ($F_{59,1118} = 1.9$; $P < .001$). Whereas the tonic EMG level was modulated by the non-REM/REM sleep cycles in BL, no clear ultradian variation was evident in P5 (Figure 3B).

To quantify eye movements during sleep in BL and P5, the variance of the EOG signal was analyzed. To eliminate the contamination of the EOG by the EEG, the ratio of the EOG variance divided by the EEG variance was computed for consecutive 5-minute intervals. The EOG/EEG variance exhibited low values in non-REM sleep and high values in REM sleep, with a prominent ultradian modulation in BL (Figure 3C). A significantly different time course was seen in P5 (2-way ANOVA; treatment [BL and P5]: $F_{1,1239} = 38.8$; time bin [1-60]: $F_{59,1239} = 5.0$; treatment \times time bin: $F_{59,1239} = 5.0$; $P < .001$ for all).

COMMENT

The results of this study confirm those of earlier studies^{30-32,34,43} that phenelzine therapy can safely eliminate REM sleep in depressed patients without altering the duration of visually scored slow-wave sleep. Our investigation is the first to conduct a detailed computer-assisted analysis of the sleep EEG before and after administration of an MAO inhibitor in humans or animals. It demonstrates that abolition of REM sleep by phenelzine treatment does not alter the intensity of non-REM sleep or the exponential decline of SWA during sleep. These observations have important implications for models of sleep regulation and hypotheses on the mechanisms of antidepressant drugs.

It is generally assumed that MAO inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors enhance postsynaptic neurotransmission of serotonin, norepinephrine, and, possibly, other neurotransmitters. Serotonin may hyperpolarize cholinergic neurons in the laterodorsal and pedunculopontine tegmental nuclei,⁴⁴ and its increased concentration in the brainstem⁴⁵ may underlie the phenelzine-induced suppression of REM sleep. Some authors⁴⁶ suggest that the changes of visually scored sleep during antidepressant therapy mainly reflect the absence of muscular atonia during REM sleep. In support of this view and in accordance with qualitative observations in early studies,³⁰ we found a significant increase in tonic EMG activity during sleep under phenelzine therapy. Nevertheless, our data demonstrate that the suppression of REM sleep

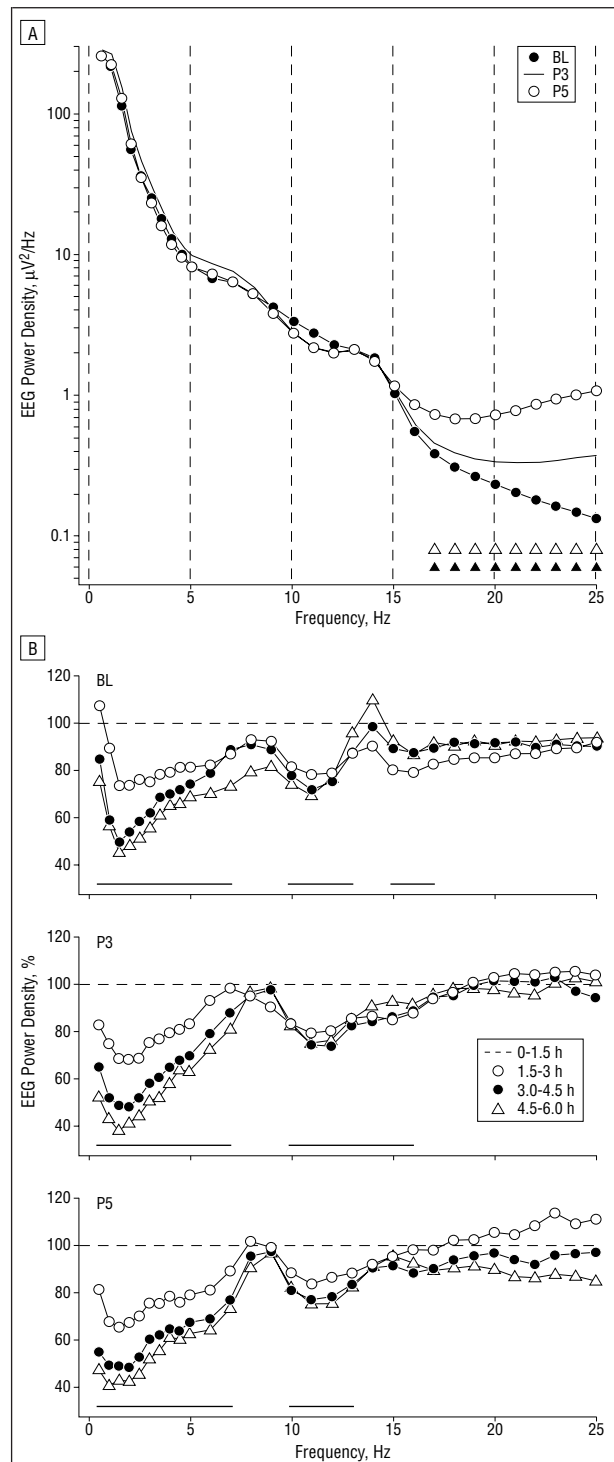


Figure 1. Electroencephalographic (EEG) power spectra in non-rapid eye movement (REM) sleep (stages 2, 3, and 4) at baseline (BL) and during weeks 3 and 4 (P3) and 5 and 6 (P5) of phenelzine treatment. A, Absolute all-night power density in each frequency bin between 0.25 and 25 Hz. The triangles above the abscissa indicate frequency bins for which power was significantly higher in P5 than in BL (solid triangles) and P3 (open triangles) ($P < .05$, 2-tailed paired t tests). B, Changes in EEG power density in non-REM sleep during consecutive 90-minute intervals in BL (top), P3 (middle), and P5 (bottom). Values of the second, third, and fourth 90-minute intervals were expressed as a percentage of the corresponding value in the first 90-minute interval (horizontal dashed lines at 100%). Horizontal lines above the abscissae indicate frequency bins for which a 1-way repeated-measures analysis of variance on log-transformed absolute power values revealed a significant effect of the within factor "interval" (1-4) ($df = 3, 30$; $P < .05$).

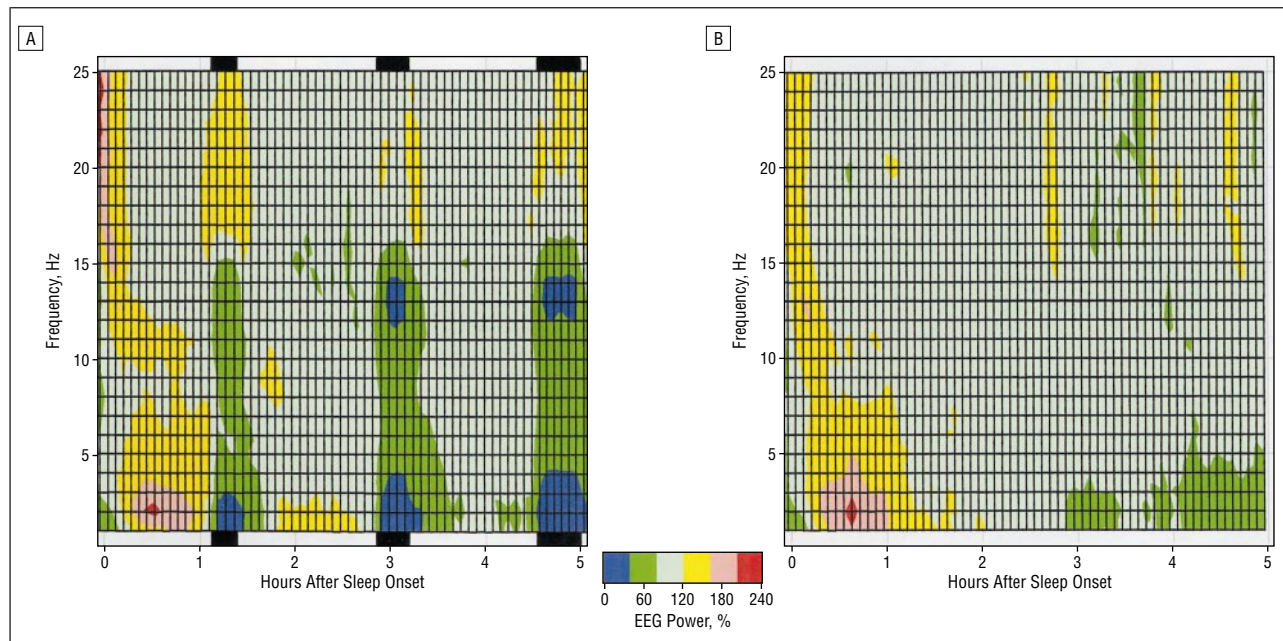


Figure 2. Color-coded relative electroencephalographic (EEG) power density in 1-Hz bins as a function of time and frequency at baseline (BL) (A) and during weeks 5 and 6 of phenelzine treatment (P5) (B). Power density in each frequency bin was expressed as a percentage of the corresponding all-night mean value in non-rapid eye movement (REM) sleep (stages 2, 3, and 4). At BL, individual non-REM and REM sleep episodes were subdivided into equal time bins such that a bin represented approximately 5 minutes. Data were aligned with respect to sleep onset (ie, the first occurrence of stage 2), averaged across patients ($n=11$), and plotted against the mean timing of non-REM and REM sleep episodes. Horizontal black bars at the top and bottom indicate REM sleep. In P5, the first 5 hours after sleep onset were subdivided into 60 five-minute intervals. Data were aligned with respect to sleep onset and averaged across patients.

is not merely due to a drug-induced dissociation of REM sleep phenomena but also includes abolishment of the typical EEG and EOG signs of this sleep state. In non-REM sleep, the effect of phenelzine therapy was limited to prolonged stage 2 and enhanced EEG power in the beta frequency range (Figure 1). Because the latter effect was restricted to P5 and paralleled the increase in tonic EMG activity, it is tempting to assume that it represents the contamination of the EEG spectrum by the sustained contraction of craniofacial muscles during sleep. It has been shown that artifacts in EEG power spectra due to muscle contractions are restricted to frequencies higher than 14 Hz.⁴⁷

The suppression of REM sleep during phenelzine treatment revealed the natural course of SWA in the absence of normal non-REM/REM sleep cycles. Power in the low-frequency EEG bands rose normally after sleep onset and then declined in an exponential manner in the absence of REM sleep. This time course (Figure 4) is reminiscent of the plasma pharmacokinetics of an orally administered drug. From the shape of this curve, we could speculate that sleep onset initiates a process or the release of an unknown SWA-promoting factor, which reaches a peak within the first hours of sleep and then declines exponentially over the course of the sleep episode. This formulation is consistent with process S in the 2-process model.^{10,23,48} REM sleep, on the other hand, could reflect an ultradian process, which interrupts or inhibits the basic mechanism underlying process S with a period of 80 to 120 minutes. If there exists an underlying ultradian oscillator of REM sleep, the neural mechanisms have not yet been identified. A regular rhythm of nocturnal penile tumescence has been reported in MAO inhibitor-treated depressed patients without REM sleep⁴⁹⁻⁵¹ and in a man who no longer had REM sleep after experiencing a shrapnel wound to his brainstem.^{52,53} These reports may suggest

that an underlying ultradian rhythm may persist even if REM sleep is abolished. It cannot be excluded from our data that averaging over patients has obliterated a weak ultradian modulation of EEG, EOG, or EMG variables in P5.

The present results do not support the REM sleep deprivation^{19,20} or the non-REM sleep deprivation hypotheses²⁴ for the mechanism of antidepressant therapies. The REM sleep suppressive effect of phenelzine did not correlate with its antidepressant effect, and SWA did not change during treatment. On the contrary, slow-wave sleep tended to increase during treatment (Table 2).

With regard to dream recall, the present data suggest that dreaming occurs in the absence of REM sleep. Use of phenelzine had different effects on the frequency of dream recall in treatment responders and nonresponders (Table 3). Specifically, a significant reduction in dreaming was found only in responders. In contrast, nonresponders remembered only a few dreams at the beginning of phenelzine administration and showed an increasing trend in dream recall during treatment. Unpleasant dreams toward the end of the night have been associated with impaired mood regulation during sleep.⁵⁴

Our findings suggest that adults can live without REM sleep without obvious harm. If anything, our responders were better because their depression was successfully treated. Lavie et al^{52,53} described a man without REM sleep for many years. He conducted a normal life and graduated from law school after wounding his brainstem. In contrast to these observations in humans, selective REM sleep deprivation for 3 to 7 weeks in rats, with the disk over water method, has been associated with death.⁵⁵ The mechanism of death in rats is unknown. These studies highlight how little is known about the basic functions of sleep in general and REM sleep in particular.

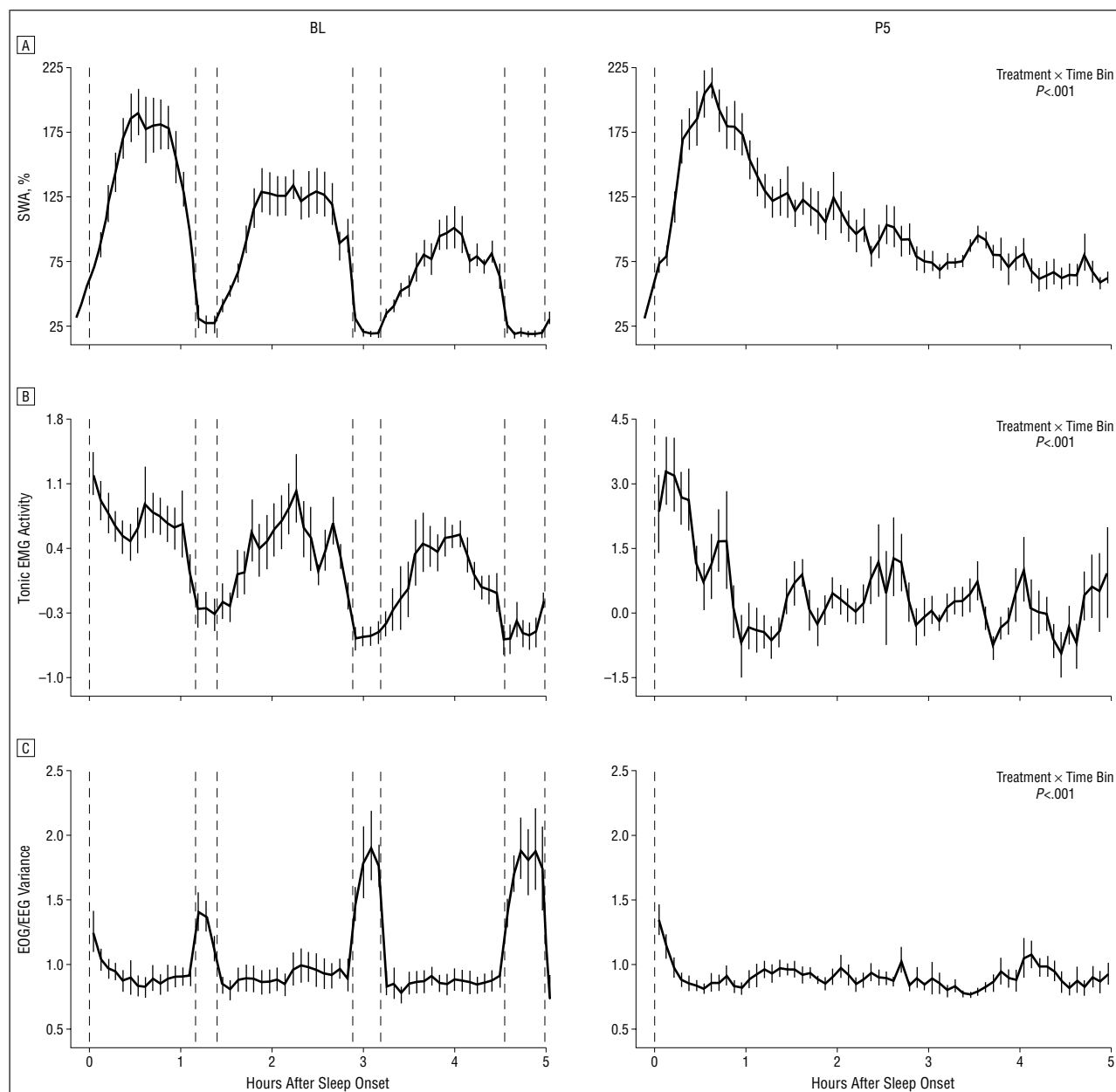


Figure 3. Time course of electroencephalographic (EEG) slow-wave activity (SWA) (power within 0.75-4.5 Hz) (A), tonic electromyographic (EMG) activity (B), and electro-oculogram (EOG)/EEG variance (C) at baseline (BL) and during weeks 5 and 6 of phenelzine treatment (P5). Relative SWA values were expressed as a percentage of the corresponding all-night value in non-rapid eye movement (REM) sleep (stages 2, 3, and 4). Tonic EMG activity was standardized with respect to the corresponding median of all 20-second values of the variance of the EMG signal during sleep (stages 1, 2, 3, and 4 and REM sleep). Subdivisions of non-REM and REM sleep episodes at BL, and of the first 5 hours of sleep in P5, are the same as in Figure 2. Vertical bars indicate ± 1 SEM; dashed vertical lines, sleep onset and delimit REM sleep episodes. Please note the different scaling of the ordinate for tonic EMG activity in the 2 groups.

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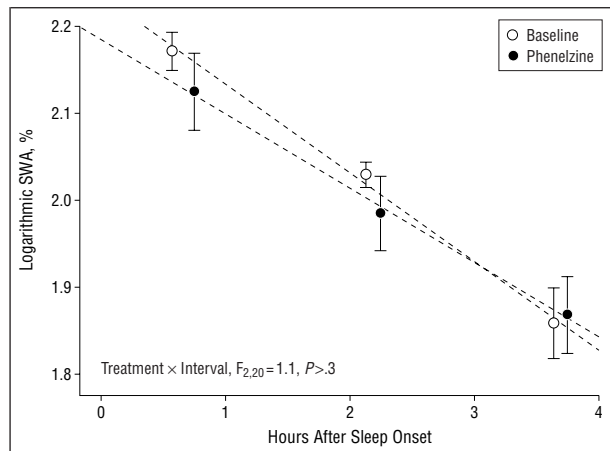


Figure 4. Mean electroencephalographic slow-wave activity (SWA) (power within 0.75-4.5 Hz) in non-rapid eye movement (REM) sleep (stages 2, 3, and 4) across the first 3 non-REM sleep episodes at baseline and across the first three 90-minute intervals after sleep onset during treatment with phenelzine. Relative SWA values, expressed as a percentage of the mean nocturnal value in non-REM sleep, were plotted on a logarithmic scale at the midpoints of the first 3 non-REM sleep episodes or 90-minute intervals. Error bars represent ± 1 SEM ($n=11$). Linear regression lines were drawn through the mean values in each group.

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